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Could Pomegranate Fight Against SARS-CoV-2?

Sally Elnawasany

Abstract

Pomegranate, *Punica granatum* L., is an authentic, generous fruit which is cultivated in many parts of the world for thousand years. The divine fruit was born from nature to provide humanity with its effluent benefits for life and health. Through the ages, Pomegranate occupied an eminent place in ayurvedic medicine. It was prescribed for treatment of parasitic infection, diarrhea, and ulcers. Pomegranate wealth of prolific pharmacological activities makes it a rich culture for multiple studies in recent years. It will not be surprising if Pomegranate provides humans with a possible help in SARS-CoV-2 pandemic. The enemy that has raided the world since the end of 2019.

Keywords: ayurvedic medicine, phytochemicals, pomegranate, SARS-CoV-2

1. Introduction

Pomegranate (*Punica granatum* L.) is a common authentic fruit that is consumed for its health benefits in the globe. It contains many phytochemical constituents mainly Phenolic compounds which are responsible for most of its pharmacological properties [1, 2]. Several studies roamed in the Pomegranate field for its therapeutic benefits; anti-inflammatory, anti-oxidant, anti-cancer, anti-viral and immune modulation activities [3]. The fact that put pomegranate on the top of phytochemical agents with possible anti SARS-CoV-2 potential. Which has been attacking the earth for over a year. It is one of Coronaviruses, member of the subfamily Coronavirinae in the family Coronaviridae and the order Nidovirales [4].

2. Severe acute respiratory syndrome coronavirus-2, SARS-CoV-2

Corona viruses are wide group of viruses of humans as well as some animals. The clinical impact is ranged from mild to severe respiratory disease. In the last two decades, the world faced two aggressive coronaviruses: severe acute respiratory syndrome coronavirus (SARS-COV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-COV) in 2012 [4]. At the end of 2019, SARS-CoV-2 was reported in China, as an abnormal highly contagious viral pneumonia. Then shortly, the virus invaded the whole world [5, 6]. SARS-CoV-2 is an enveloped positive-sense single stranded RNA virus. It consists of four subunits, spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein and nucleocapsid (N) protein [7]. Spike S protein with its two subunits, S1 and S2 is responsible for epithelial cell entry after its attachment to Angiotensin Converting

Enzyme 2, ACE2 receptors which is widely present in the respiratory tract and other parts of the body [8, 9]. While surface S1 subunit (specifically at receptor-binding domain, RBD region) attach to ACE2 receptor, transmembrane subunit (S2) starts membrane fusion between the virus and epithelial cell and begins endocytosis. This process is enabled by the two host cell enzymes; furin and transmembrane serine protease 2 (TMPRSS2) that cleaves S glycoprotein at S1/S2 [10, 11]. Then SARS-CoV-2 replicates and spreads down to the airways and occupies alveolar epithelial cells. Viral replication induces Intense immune response (Cytokine storm syndrome) with subsequent acute respiratory distress syndrome and respiratory failure, the main cause of death [12]. Treating SARS-CoV-2 infection is not easy, as we have not only to fight the virus and manage its respiratory sequelae, but we need to downregulate the hyper stimulated immune response as well. For this war, many agents have been recruited in different ways. Starting from Inhibition of virus entry as Umifenovir (Arbidol) that interferes with interaction between the viral S protein and ACE2 and block membrane fusion [13, 14]. Chloroquine and hydroxy-chloroquine (two drugs of plant origin) are also thought to inhibit viral entry but with controversial results [15, 16]. Using soluble recombinant hACE2, specific monoclonal antibodies to occupy ACE2 receptors is another method to counter act viral entry [17, 18]. Inhibition of virus replication is another modality for treatment. There are numerous trials on remdesivir [15], favipiravir [19], ribavirin, lopinavir and ritonavir to inhibit viral replication [20]. Since SARS-CoV-2 over stimulates the immune response causing what is called, cytokine storm syndrome [21]. Immune modulation is a promising target for treatment. Dexamethasone decreased mortality in mechanically ventilated and oxygen receiving patients [22]. Plasma from recovered patients, convalescent plasma-derived hyperimmune globulin and monoclonal antibodies targeting SARS-CoV-2 were also tried in many trials [23–26]. Interleukin-6 (IL-6) has an important role in the inflammatory response. Tocilizumab, interleukin-6 (IL-6) receptor-specific antibody downregulated the immune response in small trials [27, 28]. Moreover, inhibition of pro inflammatory Complement 5 by Eculizumab, a specific monoclonal antibody, helped to decrease pulmonary oedema in severe COVID-19 patients [29]. Interferon plays a role in reducing of viral replication, type I interferons provide a treatment options in COVID-19 infection [30, 31]. Protein kinases inhibitors as Baricitinib, a reversible Janus-associated kinase (JAK)-inhibitor can help in SARS-CoV-2 treatment through its anti-inflammatory, anti-viral and antifibrotic properties [32]. Baricitinib attenuated cytokine signaling in COVID-19 immune response. It also interfered with viral cell entry [33]. In another study, it improved with corticosteroids the respiration in SARS-CoV-2 pneumonia [34]. In addition, the Abl tyrosine kinase inhibitor (ATKI), imatinib was found to block viral fusion through attachment to receptor-binding domain (RBD) of SARS-CoV-2 spike protein [35]. In spite of all the previous treatment modalities, there is no proven curative agent for SARS-CoV-2 infection [36]. Which necessitates a continuous and hard search for new therapeutic agents including natural agents.

3. Could pomegranate fight against SARS-CoV-2?

3.1 Anti-viral action of pomegranate

Pomegranate attenuates many viruses [37]. Polyphenols and ellagic acid were proved to neutralized envelope virus via binding to the envelope lipid or sugar moieties [38]. Pomegranate juice succeeded to prevent Human immune deficiency virus-1 (HIV-1) cell entry by blocking CD4 and coreceptors CXCR4/CCR5

binding [39]. Ellagitannins of Pomegranate extract; punicalagin, punicalin and ellagic acid blocked the HCV NS3/4A protease activity in an in vitro study [40]. Furthermore, the activity of adenovirus was suppressed by Pomegranate peel ethanol extract on HeLa cell line. The 50% inhibitory concentration (IC₅₀) and 50% Cytotoxicity Concentration (CC₅₀) were 165 ± 10.1 and 18.6 ± 6.7 $\mu\text{g/ml}$, respectively [41]. In addition, Pomegranate juice and pomegranate polyphenol extract reduced viral titer of noroviruses with other foodborne viral surrogates [42]. A viricidal effect of Pomegranate powder extract with 800 $\mu\text{g/ml}$ polyphenols was clarified. When the titer of influenza virus (PR8 (H1N1), X31 (H3N2), and a reassortant H5N1 virus of human isolate lowered by 3log in 5 min treatment at room temperature. This effect was explored by electron microscopy when disruption of viral structure appeared [43]. Moreover, the replication and agglutination of chicken RBC's by influenza virus was inhibited by Punicalagin, a phenol in pomegranate extract. Synergistic effect was noticed in oseltamivir combination [44]. The anti Influenza mechanism was emphasized in another study where Pomegranate peel ethyl alcohol extract (PPE) inhibited the influenza virus adsorption and replication though attenuation of viral polymerase activity and protein expression [45].

3.2 Immune modulatory action of pomegranate

Mast cells and basophils have a crucial role in inflammatory and immune response [46]. These cells release pro-inflammatory cytokines TNF- α , IL-6, IL-8, histamine which initiate acute- and late-phase inflammatory response [47]. Cytokine expression is induced by many pathways such as extra-cellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) and Nuclear factor (NF)- κB [48–50]. Immune modulation action of pomegranate was confirmed in many studies. Pomegranate fruit extract strongly attenuated phorbol-12-myristate 13-acetate plus calcium ionophore A23187 (PMACI) induced inflammatory gene expression and reduced the release of interleukin (IL)-6 and IL-8 in the myeloid pre-cursor cell line KU812 cells. Through its action on c-jun N-terminal kinase (JNK), extracellular-regulated kinase (ERK) and Nuclear factor Kappa β (NF- κB) dependent pathways [51]. NF- κB signaling stimulation is mediated by IL-1 β binding to its specific cell surface receptor that activates IKKs with subsequent phosphorylation and degradation of I κB . This cascade was suppressed in human chondrocyte by pomegranate extract. Which interfered with the mRNA and protein expression of IL-6 and downregulated the activation of NF- κB /p65. Through inhibition of the IL-1 β -mediated phosphorylation of IKK β , expression of IKK β mRNA and degradation of I $\kappa\text{B}\alpha$ [52]. Moreover, in another in vitro study, Pomegranate flower (PFE) ethanol extract reduced IL-6, IL-1 β and TNF- α production with IC₅₀ value of 48.7, 71.3 and 62.5 $\mu\text{g/mL}$ respectively, in lipo-poly saccharides (LPS) -induced RAW264.7 cell macrophage. This effect was attributed to inhibition of phosphorylation of mitogen-activated protein kinase (MAPK) subgroups, extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and P38 and translocation of the NF- κB p65 subunit [53]. Pomegranate peel extract decreased the secretion of CXCL8 in both Caco-2 cells and colonic explants. Furthermore, it attenuated the expression of IL 1A, IL 6 and CXCL8 in lipopoly saccharide, LPS stimulated colonic tissues at a concentration of 5 g/ml [54].

3.3 Anti-tyrosine kinase action of pomegranate

Janus kinase (JAK) is a member of the non-receptor tyrosine kinase family. It triggers many inflammatory signaling pathways like signal transducer and activation of transcription (STAT) that induce chemotaxis of inflammatory cells such

as mast cells, T cell, B cells, macrophages [55]. Baricitinib is a Janus kinase (JAK) inhibitor and is a numb-associated kinase NAK inhibitor which attenuates AP2-associated protein kinase-1 (AAK1), the protein that promotes viral endocytosis [56, 57]. Fortunately, Pomegranate shares Baricitinib its janus kinase inhibitory action. The fact that introduces Pomegranate as a possible treating agent of SARS-CoV-2. This action was highlighted in a study where Pomegranate leaf extract antagonized Janus Kinase1 (JAK1) enzyme activity in macrophage raw cells [58]. In another study, among ellagitannins containing fruits, pomegranate was the superior in JAK2 inhibition [59].

3.4 Anti-converting enzyme (ACE) action of Pomegranate

The renin-angiotensin-aldosterone system, RAAS organizes blood pressure, fluid balance and controls the vascular response to inflammation [60]. Imbalance in that system induces hypertension, fluid retention, and inflammatory and thrombotic complications [61]. Juxtaglomerular apparatus of the kidney secretes renin which acts on angiotensinogen to form Angiotensin I (A1). Angiotensin-converting enzyme (ACE) breaks AI to AII. Angiotensin II is the main controlling agent of RAAS through stimulation of type 1 receptor (AT₁ receptor) with subsequent vasoconstriction, water retention and inflammation. While The type 2 receptor, ATR2 counteract these effects [62]. ACE2 counterbalance ACE actions. It breaks down AI into angiotensin 1-9(A1-9), and AII into angiotensin 1-7(A1-7) which has vasodilator and anti-proliferative action [63]. The renin-angiotensin system is claimed to induce severe acute lung injury in SARS-CoV-2 infection and ACE2 protects against acute lung failure and its deficiency is associated with lung damage [64]. Binding of SARS-Cov-2 to ACE2 receptor attenuates ACE2 action with subsequent lung damage [65]. On that basis, soluble ACE2 was supposed to be a possible approach for coronavirus infection [66]. It was speculated that, The use of ACE Inhibitors is associated with increased concentration of angiotensin I which upregulates ACE2 [67]. It is ambiguous, whether this postulate increases the probability of SARS-CoV-2 infection. Or ACE2 upregulation will be beneficial for counterbalance the ACE2 virus-induced downregulation with improvement of lung defense [65]. Although the role of Angiotensin converting enzyme, ACE inhibitors in SARS-CoV-2 infection is controversial, Pomegranate has the potential of ACE inhibition and may help in this battle. *Punica granatum* juice extract lowered ACE level and mean arterial blood pressure. When it was given in a dose of (PJ- 100 mg/kg and 300 mg/kg; p.o.) in angiotensin-II treated rats for 4 weeks [68]. Similar effect was emphasized in a parallel study. When Pomegranate peel extract was administered to female rats for 30 days. It inhibited coronary angiotensin-converting enzyme (ACE) activity and oxidative stress [69]. In a clinical trial, Pomegranate juice reduced serum ACE activity and systolic blood pressure in hypertensive patients when it was consumed for 2 weeks at a dose of (50 ml, 1.5 mmol of total polyphenols per day) [70].

3.5 Anti-SARS-CoV-2 action of pomegranate

Pomegranate potentials against SARS-CoV-2 infection have been investigated in many studies.

3.5.1 Anti-SARS-CoV-2 action of pomegranate

In a Computational study, Pomegranate peel extracts components; ellagic acid, gallic acid and specially punicalagin, punicalin showed promising anti SARS-CoV-2 activity through interaction with SARS-CoV-2 spike glycoprotein, angiotensin

converting enzyme 2, furin and transmembrane serine protease2. They formed more stable complexes with amino acid residues at the active sites of the selected protein targets in comparison to positive controls (umifenovir, lopinavir, camostat) with more significant binding affinity. Punicalin showed the most potent interaction with the S glycoprotein with free binding energy of -7.406 kcal/mol. All Pomegranate components ligands exerted a significant binding affinity at the ACE2 predicted active site. Furthermore, they formed the most stable complexes with furin. Amazingly, Punicalagin and punicalin strongly interacted with TMPRSS2 amino acid residues at the predicted active site by binding energy values of -7.358 and -8.168 kcal/mol, respectively with higher affinity for the target protein than camostat (-7.069 kcal/mol). [71]. In an in vitro study, Pomegranate juice reduced the infectivity of SARS-CoV-2 and influenza virus in VeroE6 cells [72]. In another study, Pomegranate peel extract showed an ability to block the binding between SARS-CoV-2 Spike glycoprotein and the human Angiotensin-Converting Enzyme 2 (ACE2) receptor, furthermore, it downregulated the activity of the virus bind 3-chymotrypsin-like cysteine protease ($3CL^{Pro}$) (an enzyme which is important for viral replication) [73].

3.5.2 Anti-SARS-CoV-2 action of natural compounds that are found in pomegranate

In a virtual study, pedunculagin, tercatatin, and castalin (hydrolysable tannins) showed an ability to bind ($3CL^{Pro}$) catalytic site that is involved in SARS-CoV-2 replication. Which sheds the light on tannins as possible anti SARS-CoV-2 agents [74]. Other virtual study investigated the action of natural compounds on SARS-CoV-2 Spike protein, viral Protease and RNA-dependent RNA polymerase and host cell protease TMPRSS2. Triterpenoids was found to be the superior in blocking the Spike protein binding site of SARS-CoV-2 [75].

4. Conclusion

Pomegranate is still surprising the world by its great therapeutic benefits. This chapter highlights the anti-SARS-CoV-2 potentials of Pomegranate. Where Anti-viral, immune modulation, tyrosine kinase and ACE inhibition actions, all enable Pomegranate to fight in this war. Further future studies are needed to confirm the utility of Pomegranate in treating SARS-CoV-2 infection.

Conflict of interest

I confirm that there are no conflicts of interest.

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